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# Anatomical MRI of the Developing Human Brain: What Have We Learned?

SARAH DURSTON, M.S., HILLEKE E. HULSHOFF POL, PH.D., B.J. CASEY, PH.D., JAY N. GIEDD, M.D., JAN K. BUITELAAR, M.D., PH.D., AND HERMAN VAN ENGELAND, M.D., PH.D.

**ABSTRACT**

**Objective:** To critically review and integrate the existing literature on magnetic resonance imaging (MRI) studies of the normally developing brain in childhood and adolescence and discuss the implications for clinical MRI studies. **Method:** Changes in regional brain volume with age and differences between the sexes are summarized from reports in refereed journal articles pertaining to MRI of the developing human brain. **Results:** White matter volume increases with age. Gray matter volumes increase during childhood and then decrease before adulthood. On average, boys have larger brains than girls; after correction for overall brain volume the caudate is relatively larger in girls, and the amygdala is relatively larger in boys. Differences are of clinical interest given gender-related differences in the age of onset, symptomatology, and prevalence noted for nearly all childhood-onset psychiatric disorders. Attention-deficit/hyperactivity disorder is frequently used as an example to demonstrate these points. **Conclusions:** Understanding the developmental trajectories of normal brain development and differences between the sexes is important for the interpretation of clinical imaging studies. *J. Am. Acad. Child Adolesc. Psychiatry*, 2001, 40(9):1012–1020. **Key Words:** brain, development, magnetic resonance imaging, review.

Advances in neuroimaging techniques have opened unprecedented access to the developing human brain. Magnetic resonance imaging (MRI) is particularly well suited to the study of children as it provides exquisitely accurate anatomical images without the use of ionizing radiation. This permits not only scanning of children, but also repeated scanning of the same individual over time. This allows us to explore the relationship between the significant leaps in motor, cognitive, and social learning that take place during childhood and adolescence (Dawson and Fischer, 1994) and the functional maturation of the neural networks that subserve these functions. Although the field of pediatric neuroimaging is in its infancy, a number of studies have been conducted to map the anatomical course of normal pediatric brain development. To our knowledge this is the first review of these normative studies.

This article complements several recent reviews of clinical neuroimaging studies, including those by Eliez and Reiss (2000) and Hendren et al. (2000). Those reviews provide an overview of imaging methods and studies of attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, Tourette's syndrome, childhood-onset schizophrenia, childhood depression, autism, and anorexia nervosa, reporting abnormalities in size or symmetry of brain regions relative to matched controls. The clinical relevance of differences in volume between groups is most obvious when the normal developmental trajectories have been charted (Giedd et al., 1996a). For example, Castellanos et al. (1996) demonstrated a loss of normal age-related decrease in volume and normal asymmetry of the caudate nucleus in ADHD, as well as volume loss in right striatal and anterior frontal areas, indicating a deviation from normal development of right frontostriatal systems in ADHD. Thus the characterization of normal brain development during a period when a number of developmental disorders emerge is important for our understanding of the underlying mechanisms and possible etiology of these disorders.

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The current review discusses MRI studies of the normally developing brain in the context of interpreting clinical studies. We underscore the importance of relating changes in brain morphometry to specific behaviors and symptomatology in neuropsychiatric disorders. Changes in regional brain volume with age and differences between the sexes are discussed. These differences are important to consider in relation to the differences in age of onset, symptomatology, and prevalence observed between the sexes for nearly all neuropsychiatric disorders. Thus gender- and timing-specific aspects of development may prove important in understanding the neural basis of these disorders. This review covers the most reliable findings reported to date and raises questions regarding the reliability and validity of measures, sample selection biases, lack of longitudinal data, and lack of behavioral correlates, all issues that should be considered in relation to the interpretation of clinical imaging studies.

## METHOD

The articles summarized were retrieved through *Medline* and included healthy subjects younger than 18 years of age (Table 1). *Healthy* is defined as either normal volunteers or, in some cases, nonpsychiatric patients. Twenty-two articles were included. Fifteen nor-

**TABLE 1**
Studies of Normal Development

| Study | Structures | Age[a] | No.[b] | Screening[c] |
|---|---|---|---|---|
| Courchesne et al., 2000 | Total brain, gray matter, white matter | 1–12, 12–80 | 50, 66 | Screened |
| Gilbert et al., 2000 | Intracranial volume, thalamus | 8–17 | 21 | Screened |
| Thompson et al., 2000 | Total brain, corpus callosum, ventricles, caudate | 3–15 | 6 | Screened |
| Giedd et al., 1999[a] | Total brain, white matter, gray matter | 4–20 | 145 | Screened |
| Giedd et al., 1999[b] | Total brain, corpus callosum | 4–18 | 139 | Screened |
| Paus et al., 1999 | White matter tracts | 4–17 | 111 | Screened |
| Pfluger et al.[(total brain)], 1999[d] | Total brain, hippocampus | 0–15 | 50 | Selected scans |
| Sowell et al., 1999 | Total brain, gray matter, white matter, CSF | 7–10, 12–16 | 9, 9 | Screened |
| Szabo et al., 1999[d] | Hippocampus | 1–7 | 11 | Selected scans |
| Utsunomiya et al., 1999[d] | Hippocampus, temporal lobe | 0–14 | 42 | Selected scans |
| Filipek et al., 1997 | Total brain, white matter, lateral ventricles, caudate, hippocampus, amygdala | 8–19 | 15 | Screened |
| Giedd, 1997 | Total brain, lateral ventricles, corpus callosum, caudate, putamen, globus pallidus, amygdala, hippocampus, temporal lobe | 4–18 | 129 | Screened |
| Giedd et al., 1997 | Total brain, lateral ventricles, corpus callosum, caudate, putamen, globus pallidus, amygdala, hippocampus, temporal lobe | 4–18 | 121 | Screened |
| Caviness et al., 1996 | Total brain, cerebellum, ventricular system, white matter, caudate, putamen, palladum, hippocampus, amygdala | 7–11, 17–33 | 30, 20 | Screened |
| Giedd et al., 1996[a] | Total brain, corpus callosum | 4–18 | 114 | Screened |
| Giedd et al., 1996[b] | Total brain, cerebellum, lateral ventricles, caudate, putamen, globus pallidus | 4–18 | 104 | Screened |
| Giedd et al., 1996[c] | Total brain, amygdala, hippocampus, temporal lobe | 4–18 | 99 | Screened |
| Reiss et al., 1996[d] | Total brain, gray matter, white matter, caudate, CSF | 5–17 | 85 | Screened |
| Pfefferbaum et al., 1994[d] | Gray matter, white matter, CSF | 0–30 | 88 | Selected scans |
| Rauch and Jinkins, 1994[d] | Corpus callosum | 0–19, 20–87 | 45, 117 | Selected scans |
| Pujol et al., 1993[d] | Corpus callosum | 11–61 | 90 | Selected scans |
| Allen et al., 1991[d] | Corpus callosum | 2–15, 16–80 | 24, 122 | Selected scans |
| Jernigan et al., 1991[d] | Gray matter, white matter, caudate, CSF | 8–20, 21–35 | 23, 16 | Screened |
| Jernigan and Tallal, 1990[d] | Gray matter, white matter, caudate, CSF | 8–10, 25–39 | 15, 9 | Screened |
| Schaefer et al., 1990[d] | Corpus callosum | 0–20 | 95 | Selected scans |

*Note:* CSF = cerebrospinal fluid.
[a] Ages of subjects included in the study (in years).
[b] Number of subjects included. If the subjects were split into groups by age, the numbers in this column refer to each age group in the previous column.
[c] Subjects were either screened before inclusion (screened), or magnetic resonance imaging scans that had been read as normal were included in the study (selected scans).
[d] Slice thickness >3.0 mm.

mative articles were excluded as they reported qualitative or area measures rather than quantitative or volumetric measures. The only exception was studies of the corpus callosum, as all relied on area measures. Thirty-five articles about childhood disorders were also reviewed. Three of these were included, as they reported their results for control subjects but had not published them separately. Measurements were based on $T_1$-weighted scans with slice thickness of between 1.5 mm and 7.5 mm. Several papers report data for an overlapping group of subjects (e.g., Giedd, 1997; Giedd et al., 1999a,b, 1997, 1996a–c; Paus et al., 1999; Thompson et al., 2000).

Findings are summarized in Tables 2 and 3. Differences are discussed in terms of change in regional brain volume with age and differences between the sexes. Where possible, estimates of percent difference in volume are given. Percentages are based on data provided or were estimated from graphs and regression lines given in the original reports. Differences associated with age are always between the youngest and oldest in the sample. Cerebrum, excluding the cerebellum, is often used instead of total brain volume. Some reports included cerebrospinal fluid in these measures.

## RESULTS

### Developmental Changes

Consistent with postmortem studies (Kretschmann et al., 1986), total brain size does not increase significantly after age 5. This relative stability of total brain volume belies a dynamic interplay of simultaneously occurring progressive and regressive events, with different regions following different time courses.

White matter volume increases significantly during childhood and into adulthood. This is probably related to ongoing myelination of axons by oligodendrocytes, following a pattern throughout the brain of inferior to superior and posterior to anterior (Yakovlev and Lecours, 1967). Reiss et al. (1996) showed the largest increase in the prefrontal region in their sample of 5–17 year olds. Much myelination occurs before birth (Grodd, 1993; Hansen et al., 1993; Wang et al., 1998) and during the first 2 years (Barkovich et al., 1988; Grodd, 1993; Holland et al., 1986; Lan et al., 2000; Martin et al., 1988; Nakagawa et al., 1998; Van der Knaap et al., 1991), but it continues throughout life (Yakovlev and Lecours, 1967). The largest white matter tract, the corpus callosum, continues to increase in size, probably because of ongoing myelination. Contrary to the typical pattern of caudal to rostral development, anterior regions, which have been related to primary sensory and motor functions, mature earlier, whereas the posterior corpus callosum areas do not mature until adolescence (Giedd et al., 1999b; Thompson et al., 2000). One explanation may be that these measurements are based on area measurement in a single midsagittal slice rather than volumetric measurements and are therefore more prone to error.

In contrast to white matter, cortical gray matter generally exhibits a net decrease in volume across this age span. Longitudinal studies suggest a childhood increase in gray matter volumes followed by a decrease before adulthood (Giedd et al., 1999a). This decrease may be due to the ongoing process of pruning and cell death among both neurons and glial cells. Most of the neuronal proliferation and selective cell death takes place in utero (Rabinowicz, 1986), although it continues during childhood and puberty (Jacobson, 1991). Neuronal cell death is thought to influence that of glial cells (Jacobson, 1991), and this may contribute to the decrease in tissue volume. As this effect is widespread, it could, in part, explain the nonspecific increase in the volume of the lateral ventricles.

Subcortical gray matter shows a similar pattern to cortical gray matter. The basal ganglia typically decrease in volume with age. Thompson et al. (2000) recently suggested that, for the caudate, most of the tissue loss takes place in the head of this structure. They used an elastic deformation algorithm to calculate the difference in surface of structures from two longitudinal scans from the same subject, and then calculated a tensor map, representing the direction and rate of growth from the volumetric deformation. In contrast to the basal ganglia, the temporal lobe structures (amygdala and hippocampus) appear to increase in volume with age. This difference is interesting from a clinical perspective, as neuropsychiatric disorders that are thought to involve the basal ganglia have an earlier age of onset (e.g., ADHD and Tourette's syndrome) than disorders involving temporal lobe structures (e.g., schizophrenia and depression) (Eliez and Reiss, 2000; Hendren et al., 2000).

### Sex Differences

On average, the male brain is 10% larger than the female brain (Table 3). Most structures in the brain display this 10% difference; however, the caudate, and possibly globus pallidus and hippocampus, are disproportionately larger in female brains, whereas the amygdala is disproportionately smaller. It is tempting to hypothesize that these differences may be mediated by sex hormones. This notion is supported by primate studies that show that the amygdala contains predominantly androgen receptors, whereas the hippocampus contains predominantly estrogen receptors (Clark et al., 1988; Morse et al., 1986; Sholl and Kim, 1989). However, other factors, such as X- or Y-chromosome effects and environmental influence, could all play a role in sex-related differences in the brain

**TABLE 2**
Developmental Changes

| | Change With Age | Difference[a] | Age[b] | No.[c] | References |
|---|---|---|---|---|---|
| Total brain | — | | 7–11 | 30 | Caviness et al., 1996 |
| | ↑ | 25% | 1–15 | 50 | Courchesne et al., 2000 |
| | — | | 4–18 | 129 | Giedd, 1997 |
| | | | | 114, 104, 99, 121 | Giedd et al., 1996a–c, 1997 |
| | | | 8–39 | 24 | Jernigan and Tallal, 1990 |
| | | | 8–35 | 39 | Jernigan et al., 1991 |
| | ↑ | 117% | 0–15 | 27 | For males (Pfluger et al., 1999) |
| | | 71% | 0–15 | 23 | For females (Pfluger et al., 1999) |
| | — | | 5–17 | 85 | Reiss et al., 1996 |
| White matter | ↑ | 16% | 7–33 | 30 | Caviness et al., 1996 |
| | | 74% | 1–15 | 50 | Courchesne et al., 2000 |
| | | 12% | 4–22 | 145 | Giedd et al., 1999a |
| | — | | 8–39 | 24 | Jernigan and Tallal, 1990 |
| | | | 8–35 | 39 | Jernigan et al., 1991 |
| | ↑ | 71% | 0–30 | 88 | Pfefferbaum et al., 1994 |
| | ↑[d] | 16% | 5–17 | 85 | Reiss et al., 1996 |
| Cortical gray matter | ↑ | 13% | 1–9 | 116 | Courchesne et al., 2000 |
| | ↓ | 28% | 9–80 | | |
| | ↑preadolescent ↓postadolescent | | 4–20 | 145 | Giedd et al., 1999a (except occipital) |
| | ↓[d] | | 8–39 | 24 | Jernigan and Tallal, 1990 |
| | | | 8–35 | 39 | In superior areas (Jernigan et al., 1991) |
| | ↑ | 13% | 0–4 | 88 | Pfefferbaum et al., 1994 |
| | ↓ | 32% | 4–30 | | |
| | ↓[d] | 23% | 5–17 | 85 | Reiss et al., 1996 |
| | ↓ | | 7–10 | 9 | In parietal & frontal areas (Sowell et al., 1999) |
| | | | 3–15 | 6 | Thompson et al., 2000 |
| Total CSF | ↑ | 160% | 1–55 | 116 | Courchesne et al., 2000 |
| Lateral ventricles | ↑ | 152% | 4–18 | 79 | For males (Giedd, 1997) |
| | | 74% | 4–18 | 79 | For females (Giedd, 1997) |
| | | 144% | 4–18 | 55 | For males only (Giedd et al., 1996b) |
| | | 63% | 4–18 | 71 | For males only (Giedd et al., 1997) |
| | | | 8–35 | 39 | Jernigan et al., 1991 |
| Ventricular CSF | ↑ | | 8–39 | 24 | Jernigan and Tallal, 1990 |
| | | | | 39 | Jernigan et al., 1991 |
| | — | | 0–30 | 88 | Pfefferbaum et al., 1994 |
| Nonventricular CSF | — | | 0–30 | 88 | Pfefferbaum et al., 1994 |
| | ↑ | 7% | 5–17 | 85 | Reiss et al., 1996 |
| Corpus callosum | ↑ | 51% | 2–15 | 24 | Allen et al., 1991 |
| | | | 4–18 | 129 | Giedd, 1997 |
| | | 31% | 4–18 | 114 | Giedd et al., 1996a |
| | | | 4–18 | 121 | Giedd et al., 1997 |
| | | 20% | 4–18 | 145 | Giedd et al., 1999a |
| | | 11% | 11–19 | 14 | Pujol et al., 1993 |
| | | 247% | 0–9 | 29 | Rauch and Jinkins, 1994 |
| | | 18% | 10–19 | 16 | |
| | ↑[e] | 33% | 0–20 | 95 | Schaefer et al., 1990 |
| Caudate | ↓ | 15% | 4–18 | 55 | For males only (Giedd et al., 1996b) |
| | ↓[d] | | 8–35 | 39 | Jernigan et al., 1991 |
| | ↓ | | 3–15 | 6 | Thompson et al., 2000 |
| Putamen | ↓ | 9% | 4–18 | 55 | For males only (Giedd et al., 1996b) |
| Globus pallidus | ↓ | | 4–18 | 71 | For males, on left only (Giedd et al., 1997) |
| | — | | 4–18 | 104 | Giedd et al., 1996b |
| Amygdala | ↑ | 53% | 4–18 | 79 | For males only (Giedd, 1997) |
| | | 45% | 4–18 | 53 | For males, on left only (Giedd et al., 1996c) |
| | | | 4–18 | 71 | For males only (Giedd et al., 1997) |

— *Continued*

**TABLE 2**
*(Continued)*

| | Change With Age | Difference[a] | Age[b] | No.[c] | References |
|---|---|---|---|---|---|
| Hippocampus | ↑ | 12% | 4–18 | 50 | For females only (Giedd, 1997) |
| | | 20% | 4–18 | 46 | For females, on right only (Giedd et al., 1996c) |
| | | | 4–18 | 121 | Giedd et al., 1997 |
| | | 100% | 0–15 | 50 | Pfluger et al., 1999 |
| | | | 1–7 | 11 | Szabo et al., 1999 |
| | | | 0–14 | 42 | Utsunomiya et al., 1999 |
| Temporal lobe | — | | 4–18 | 99 | Giedd et al., 1996c |
| | ↑ | | 0–14 | 42 | Utsunomiya et al., 1999 |
| Cerebellum | — | | 4–18 | 104 | Giedd et al., 1996b |
| | ↑ | | 8–39 | 24 | Jernigan and Tallal, 1990 |

*Note:* CSF = cerebrospinal fluid; ↑ = increase; ↓ = decrease; — = no change.
[a] Estimated difference is based on the youngest age compared with the oldest in the sample.
[b] Ages of subjects included in the study (in years).
[c] Number of subjects included.
[d] Corrected for total brain volume.
[e] Corrected for intracranial area.

(Jacobson, 1991). Clinically, it is interesting that the caudate nucleus is relatively larger in female brains, as this nucleus is implicated in ADHD and Tourette's syndrome, which are more common in males (Castellanos et al., 1996). Conversely, the amygdala is relatively smaller and has been implicated in affective disorders, such as depression and anxiety disorders, which are more common in females (Drevets, 2000).

## DISCUSSION

While the reviewed reports describe an increase in brain volume over the first few years, significant decreases in regional volumes and overall stability in brain size are shown to occur during later childhood and adolescence, contrary to general misconceptions of brain growth over this period. Regional changes in brain volume throughout childhood and adolescence are relevant in relation to landmarks in behavioral development and the emergence of clinical disorders over this age period.

### Relevance to Behavior

By linking emerging knowledge of anatomical development to behavioral changes in the child, we may learn more about the functional organization of the brain, its development and disruption in developmental disorders. For example, the basal ganglia have a number of projections to and from the frontal cortex and both brain regions mature relatively late (Sowell et al., 2000), presumably reflecting the development of cognitively driven actions throughout adolescence. However, few studies have linked these changes in brain development to behavior. An exception is a study by Casey et al. (1997a) that showed correlations between performance on measures of response inhibition and volumetric measures of the prefrontal cortex and basal ganglia in healthy children, that was not present or reversed, in children with ADHD. In another study of healthy children between 6 and 18 years (Casey et al., 1997b), a correlation was found between the size of the anterior cingulate gyrus—a structure that is thought to be critical in executing control—and the speed with which subjects switched attentional set. This correlation remained significant, even after controlling for age, IQ, and cerebral volume, making this study one of the first to demonstrate MRI-based anatomical correlates of normal behavior. Although such correlational analyses provide an indirect link between brain and behavior, advances in current imaging methods allow more direct linking of the two.

### New Directions and Evolving Technology

Developments in noninvasive neuroimaging present an exciting new stage in developmental science. New imaging techniques allow for novel approaches to the study of human brain function. For example, functional MRI (fMRI) utilizes a change in MR signal, caused by differences in blood oxygenation level to image activation in the brain during cognitive activity. Activity in a brain region causes inflow of fresh, oxygenated blood. This inflow results in an increase in MR signal relative to deoxygenated regions, which is known as the BOLD (or blood oxygen level dependent) signal. A difference image of the

**TABLE 3**
Sex Differences

| | Direction | Difference | Age[a] | No.[b] | References |
|---|---|---|---|---|---|
| Total Brain | M>F | 7% | 7–11 | 30 | Caviness et al., 1996 |
| | | 9% | 4–18 | 129 | Giedd, 1997 |
| | | | 4–18 | 114, 104, 99, 121 | Giedd et al., 1996a–c, 1997 |
| | | 11% | 4–18 | 139 | Giedd et al., 1999b |
| | | | 5–17 | 85 | Reiss et al., 1996 |
| White matter | M>F | 10% | 5–17 | 85 | Reiss et al., 1996 |
| Cortical gray matter | M>F | 10% | 4–22 | 145 | Giedd et al., 1999a |
| | M>F | | 0–30 | 88 | Pfefferbaum et al., 1994 |
| | M=F[c] | | | | |
| | M>F[d] | 11% | 5–17 | 85 | Reiss et al., 1996 |
| Total CSF | M=F | | 0–30 | 88 | Pfefferbaum et al., 1994 |
| Lateral ventricles | M=F | | 4–18 | 121 | Giedd et al., 1997 |
| | | | 0–30 | 88 | Pfefferbaum et al., 1994 |
| Nonventricular CSF | M<F[d] | | 5–17 | 85 | Reiss et al., 1996 |
| Corpus callosum | M=F | | 2–15 | 24 | Allen et al., 1991 |
| | M=F[d] | | 4–18 | 129 | Giedd, 1997 |
| | | | | 114, 121, 145 | Giedd et al., 1996a, 1997, 1999a |
| | M=F | | 11–61 | 90 | Pujol et al., 1993 |
| | | | 0–87 | 162 | Rauch and Jinkins, 1994 |
| Caudate | M<F[d] | | 7–11 | 30 | Caviness et al., 1996 |
| | | | 4–18 | 104, 121, 129 | Giedd et al., 1996b, 1997; Giedd, 1997 |
| Putamen | M=F[d] | | 7–11 | 30 | Caviness et al., 1996 |
| | | | 4–18 | 129, 121 | Giedd, 1997; Giedd et al., 1997 |
| | M>F[d] | | 4–18 | 104, 121 | Giedd et al., 1996b, 1997 |
| Globus pallidus | M>F[d] | | 7–11 | 30 | Caviness et al., 1996 |
| | M>F[d] | | 4–18 | 129, 104, 121 | Giedd, 1997; Giedd et al., 1996b, 1997 |
| Amygdala | M>F[d] | 19% | 7–11 | 30 | Caviness et al., 1996 |
| | | | 4–18 | 129 | Giedd, 1997 |
| | M=F[d] | | 4–18 | 99, 121 | Giedd et al., 1996c, 1997 |
| Hippocampus | M>F[d] | | 7–11 | 30 | Caviness et al., 1996 |
| | M=F[d] | | 4–18 | 99 | Giedd et al., 1996c |
| Temporal lobe | M=F[d] | | 4–18 | 99, 121 | Giedd et al., 1996c, 1997 |
| Thalamus | M=F | | 8–17 | 21 | Gilbert et al., 2000 |
| Cerebellum | M>F | 6% | 7–11 | 30 | Caviness et al., 1996 |
| | | 8% | 4–18 | 104 | Giedd et al., 1996b |
| | | | 8–39 | 24 | Jernigan and Tallal, 1990 |

*Note:* CSF = cerebrospinal fluid; M = male; F = female.
[a] Ages of subjects included in the study (in years).
[b] Number of subject included.
[c] Corrected for intracranial area.
[d] Corrected for total brain volume.

task condition compared with a baseline condition is overlaid on an anatomical MRI. This technique can help visualize which brain areas are involved in various forms of behavior. By correlating the MR signal in a given region with performance, we can assess which areas are driving a behavior or symptom. As yet, few normative developmental fMRI studies have been published (see Casey et al., 2000, for review), but the results are promising. Children show different patterns of activation than adults, recruiting either larger areas or different brain regions to perform the same task (Casey et al., 1997c). This may represent differences in functional organization, or alternatively in ability or strategy. Differences in performance can be addressed by parametrically manipulating task difficulty by varying either the speed or memory load across a task. Parametric designs like these, together with event-related fMRI, which allows individual behavioral trials to be linked to MR signal changes, are promising new approaches.

Diffusion tensor imaging (DTI) is another evolving technique that allows the tracking of white matter fiber tract development. It assesses the regularity and myelina-

tion of fibers more directly than conventional MRI by quantifying the diffusion of water molecules in the brain (Klingberg et al., 1999). As these molecules move along fibers more easily than across fibers, this technique allows for the directional mapping of white matter fiber tracts. It provides a more direct measure of myelination and has already been used successfully with developmental populations (Klingberg et al., 1999).

Genetic influences on brain development can be investigated by performing sibling and twin studies, in which brain anatomy is compared between individuals with varying levels of genetic similarity. Another approach is to correlate well-known and frequently occurring genetic polymorphisms with brain morphometry and behavior (Casey et al., 2001; Castellanos et al., 1998)

### General Limitations

A number of limitations of imaging studies need to be acknowledged in the context of both clinical and normative studies. Issues include the validity and reliability of measures (e.g., using measurements that rely on a representative slice versus whole volume or do not correct for total brain volume). Also, bias in subject selection is important (e.g., exclusion of lower socioeconomic groups through extensive screening or the inclusion of patients in the sample who have had their scans read as normal). Sample size is a major issue, as imaging techniques require considerable statistical power. For example, studies of ADHD using small sample sizes have suggested a pattern of right-greater-than-left asymmetry for the caudate nucleus, and the opposite in normal development (Hynd et al., 1993; Semrud-Clikeman et al., 2000). However, other studies of larger samples showed the reverse pattern of a loss of normal, right-greater-than-left caudate asymmetry in this disorder (Castellanos et al., 1996). The issue of small samples is especially important to keep in mind with the increasing number of imaging studies in rare disorders (e.g., Williams syndrome and autism). Finally, the key question in neuroanatomical MRI studies is what a change in the volume of a brain region in a given disorder means. Although gross differences in size or symmetry of brain structures can be quantified, individual cells and cell layers cannot yet be visualized. This means that, although the volume and shape of brain structures may be determined, the underlying cause of any differences cannot.

### Clinical Implications

Childhood psychiatric disorders are increasingly being conceptualized as neurodevelopmental in origin, although the mechanisms behind such altered development are not understood. This review illustrates how regional volumetric changes with age and sexual dimorphism of brain structures are relevant to both the age of onset and gender ratios of specific developmental disorders. Whereas the pattern of brain growth as indexed by MRI over the first 2 years is an overall increase in volume, organized development, involving both volumetric increases and decreases, takes place during later childhood and adolescence. For example, portions of the basal ganglia, such as the caudate nucleus, show gradual decreases in volume, particularly in males, between the ages of 6 and 12 years. This is clinically interesting as the basal ganglia have been implicated in a number of childhood disorders that affect males preferentially and are diagnosed during this period of development (e.g., ADHD [Castellanos et al., 1996], Tourette's syndrome [Peterson et al., 1993], obsessive-compulsive disorder [Rosenberg et al., 1997], and childhood-onset schizophrenia [Frazier et al., 1996]). Castellanos et al. (1996) report that boys with ADHD do not show the gradual decrease in caudate volume reported in normal development, but rather that the caudate begins and remains smaller across this period of development. This observation suggests that children may be predisposed to clinical disorders involving the basal ganglia during earlier developmental periods. Casey et al. (2001) report a fourfold increase in ADHD as well as the presence of tics and anxiety in school-age children with histories of perinatal insults involving the basal ganglia. Moreover, males were four times more likely than females to have a disorder. Thus this exemplifies how imaging studies can identify a sensitive period of development that may predispose a child to clinical disorders.

The sexual dimorphism reported across a number of the reviewed studies has significant clinical relevance. For example, the caudate nucleus is relatively larger in maturing females than males. As stated, this is interesting in view of the higher prevalence in males for disorders involving this nucleus. Conversely, the amygdala is relatively smaller in maturing girls and has been implicated in depression and anxiety disorders, which are more common in females (Drevets, 2000). Findings such as these suggest a vulnerability in the development of certain brain regions that differs for the sexes and may predispose them to different clinical syndromes.

Another important clinical issue is to what extent differences in the volume of brain regions relate to clinical symptomatology or its severity. As discussed previously, a few studies have started to relate MRI-based morphometry to symptomatology. This approach, combined with new technologies such as fMRI and DTI, will advance the understanding of the disruption of neural systems and their development in clinical disorders.

In sum, the study of normal brain development using MRI can aid the understanding of deviant development in childhood neuropsychiatric disorders. With the evolution of new technologies, rapid developments are being made that will allow new perspectives on the study of the developing human brain.

### Conclusions

1. Magnetic resonance imaging studies of the developing human brain reveal distinct developmental patterns, involving both regional increases and decreases in volume.
2. Clinical imaging studies may be most informative on etiology when they show how brain development in a given disorder deviates from normal patterns of development as a function of age.
3. Sexual dimorphism observed in normally developing children can suggest differential vulnerability of brain regions between the sexes that may predispose them to different clinical disorders.
4. In the interpretation of clinical imaging studies, methodological issues need to be given adequate consideration. Sample size is critical, given the large number of rare disorders currently under investigation.

## REFERENCES


Allen L, Richey M, Chai Y, Gorski R (1991), Sex differences in the corpus callosum of the living human being. *J Neurosci* 11:933–942

Barkovich AJ, Kjos BO, Jackson DE Jr, Norman D (1988), Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. *Radiology* 166:173–180

Casey BJ, Castellanos FX, Giedd JN et al. (1997a), Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 36:374–383

Casey BJ, Durston S, Fossella JA (2001), Evidence for a mechanistic model of cognitive control. *Clin Neurosci Res* 1:267–282

Casey BJ, Thomas KM, Welsh TF, Livnat R, Eccard CH (2000), Cognitive and behavioral probes of developmental landmarks, for use in functional neuroimaging. In: *Functional Neuroimaging in Child Psychiatry*, Ernst M, Rumsey JM, eds. Cambridge, England: Cambridge University Press, pp 155–168

Casey BJ, Trainor R, Giedd J et al. (1997b), The role of the anterior cingulate in automatic and controlled processes: a developmental neuroanatomical study. *Dev Psychobiol* 30:61–69

Casey BJ, Trainor R, Orendi JL et al. (1997c), A developmental functional MRI study of prefrontal activation during performance of a go-no-go task. *J Cogn Neurosci* 9:835–847

Castellanos FX, Giedd JN, Marsh WL et al. (1996), Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 53:607–616

Castellanos FX, Lau E, Tayebi N et al. (1998), Lack of an association between a dopamine-4 receptor polymorphism and attention-deficit/hyperactivity disorder: genetic and brain morphometric analyses. *Mol Psychiatry* 3:431–434

Caviness VS Jr, Kennedy DN, Richelme C, Rademacher J, Filipek PA (1996), The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. *Cereb Cortex* 6:726–736

Clark AS, MacLusky NJ, Goldman-Rakic PS (1988), Androgen binding and metabolism in the cerebral cortex of the developing rhesus monkey. *Endocrinology* 123:932–940

Courchesne E, Chisum HJ, Townsend J et al. (2000), Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. *Neuroradiology* 216:672–682

Dawson G, Fischer KW, eds (1994), *Human Behavior and the Developing Brain*. New York: Guilford

Drevets WC (2000), Neuroimaging studies of mood disorders. *Biol Psychiatry* 48:813–829

Eliez S, Reiss AL (2000), Annotation: MRI neuroimaging of childhood psychiatric disorders: a selective review. *J Child Psychol Psychiatry* 41:679–694

Filipek PA, Semrud Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN (1997), Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology* 48:589–601

Frazier JA, Giedd JN, Hamburger SD et al. (1996), Brain anatomic magnetic resonance imaging in childhood-onset schizophrenia. *Arch Gen Psychiatry* 54:617–624

Giedd JN (1997), Normal development. *Child Adolesc Psychiatr Clin N Am* 6:265–282

Giedd JN, Blumenthal J, Jeffries NO et al. (1999a), Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci* 2:861–863

Giedd JN, Blumenthal J, Jeffries NO et al. (1999b), Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. *Prog Neuropsychopharmacol Biol Psychiatry* 23:571–588

Giedd JN, Castellanos FX, Rajapakse JC, Vaituzis AC, Rapoport JL (1997), Sexual dimorphism of the developing human brain. *Prog Neuropsychopharmacol Biol Psychiatry* 21:1185–1201

Giedd JN, Rumsey JM, Castellanos FX et al. (1996a), A quantitative MRI study of the corpus callosum in children and adolescents. *Brain Res Dev Brain Res* 91:274–280

Giedd JN, Snell JW, Lange N et al. (1996b), Quantitative magnetic resonance imaging of human brain development: ages 4–18. *Cereb Cortex* 6:551–560

Giedd JN, Vaituzis AC, Hamburger SD et al. (1996c), Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4–18 years. *J Comp Neurol* 366:223–230

Gilbert AR, Moore GJ, Keshavan MS et al. (2000), Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder, who are taking paroxetine. *Arch Gen Psychiatry* 57:449–456

Grodd W (1993), Normal and abnormal patterns of myelin development of the fetal and infantile human brain using magnetic resonance imaging. *Curr Opin Neurol* 6:393–397

Hansen PE, Ballesteros MC, Soila K, Garcia L, Howard JM (1993), MR imaging of the developing human brain, part 1: prenatal development. *Radiographics* 13:21–36

Hendren RL, DeBacker I, Pandina GJ (2000), Review of neuroimaging studies of child and adolescent psychiatric disorders from the past ten years. *J Am Acad Child Adolesc Psychiatry* 39:815–828

Holland BA, Haas DK, Norman D, Brant-Zawadzki M, Newton TH (1986), MRI of normal brain maturation. *AJNR Am J Neuroradiol* 7:201–208

Hynd GW, Hern KL, Novey ES et al. (1993), Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. *J Child Neurol* 8:339–347

Jacobson M (1991), *Developmental Neurobiology*. New York: Plenum

Jernigan TL, Tallal P (1990), Late childhood changes in brain morphology observable with MRI. *Dev Med Child Neurol* 32:379–385

Jernigan TL, Trauner DA, Hesselink JR, Tallal PA (1991), Maturation of human cerebrum observed in vivo during adolescence. *Brain* 114:2037–2049

Klingberg T, Vaidya CJ, Gabrieli JD, Moseley ME, Hedehus M (1999), Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study. *Neuroreport* 10:2817–2821

Kretschmann HJ, Kammradt G, Krauthausen I, Sauer B, Wingert F (1986), Brain growth in man. *Bibl Anat* 28:1–26

Lan LM, Yamashita Y, Tang Y et al. (2000), Normal fetal brain development: MR imaging with a half-Fourier rapid acquisition with relaxation enhancement sequence. *Radiology* 215:205–210

Martin E, Kikinis R, Zuerrer M et al. (1988), Developmental stages of human brain: an MR study. *J Comput Assist Tomogr* 12:917–922

Morse JK, Scheff SW, DeKosky ST (1986), Gonadal steroids influence axonal sprouting in the hippocampal dentate gyrus: a sexually dimorphic response. *Exp Neurol* 94:649–658

Nakagawa H, Iwasaki S, Kichikawa K et al. (1998), Normal myelination of anatomic nerve fiber bundles: MR analysis. *AJNR Am J Neuroradiol* 19:1136

Paus T, Zijdenbos A, Worsley K et al. (1999), Structural maturation of neural pathways in children and adolescents: in vivo study. *Science* 283:1908–1911

Peterson B, Riddle MA, Cohen DJ et al. (1993), Reduced basal ganglia volumes in Tourette's syndrome using three-dimensional reconstruction techniques from magnetic resonance images. *Neurology* 43:941–949

Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO (1994), A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch Neurol* 51:874–887

Pfluger T, Weil S, Weis S et al. (1999), Normative volumetric data of the developing hippocampus in children based on magnetic resonance imaging. *Epilepsia* 40:414–423

Pujol J, Vendrell P, Junque C, Marti-Vilalta JL, Capdevila A (1993), When does human brain development end? Evidence of corpus callosum growth up to adulthood. *Ann Neurol* 34:71–75

Rabinowicz T (1986), The differentiated maturation of the cerebral cortex. In: *Human Growth*, Falkner F, Tanner JM, eds. New York: Plenum, pp 385–410

Rauch RA, Jinkins JR (1994), Analysis of cross-sectional area measurements of the corpus callosum adjusted for brain size in male and female subjects from childhood to adulthood. *Behav Brain Res* 64:65–78

Reiss AL, Abrams MT, Singer HS, Ross JL, Denckla MB (1996), Brain development, gender and IQ in children: a volumetric imaging study. *Brain* 119:1763–1774

Rosenberg DR, Keshavan MS, O'Hearn KM et al. (1997), Frontostriatal measurement in treatment-naïve children with obsessive-compulsive disorder. *Arch Gen Psychiatry* 54:824–830

Schaefer GB, Thompson JN Jr, Bodensteiner JB et al. (1990), Quantitative morphometric analysis of brain growth using magnetic resonance imaging. *J Child Neurol* 5:127–130

Semrud-Clikeman M, Steingard RJ, Filipek P, Biederman J, Bekken K, Renshaw PF (2000), Using MRI to examine brain–behavior relationships in males with attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry* 39:477–484

Sholl SA, Kim KL (1989), Estrogen receptors in the rhesus monkey brain during fetal development. *Brain Res Dev Brain Res* 50:189–196

Sowell ER, Thompson PM, Holmes CJ, Batth R, Jernigan TL, Toga AW (1999), Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *Neuroimage* 9:587–597

Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW (2000), In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nat Neurosci* 2:859–861

Szabo CA, Wyllie E, Siavalas EL et al. (1999), Hippocampal volumetry in children 6 years or younger: assessment of children with and without complex febrile seizures. *Epilepsy Res* 33:1–9

Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW (2000), Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature* 404:190–193

Utsunomiya H, Takano K, Okazaki M, Mitsudome A (1999), Development of the temporal lobe in infants and children: analysis by MR-based volumetry. *AJNR Am J Neuroradiol* 20:717–723

Van der Knaap MS, Valk J, Bakker CJ et al. (1991), Myelination as an expression of the functional maturity of the brain. *Dev Med Child Neurol* 33:849–857

Wang Z, Chen J, Qin Z, Zhang J (1998), The research of myelinization of normal fetal brain with magnetic resonance imaging. *Chin Med J (Engl)* 111:71–74

Yakovlev PI, Lecours A (1967), The myelogenetic cycles of regional maturation in the brain. In: *Regional Development of the Brain in Early Life*, Minkowski A, ed. Oxford, England: Blackwell, pp 3–65

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**Adolescent Girls' Sexual Attitudes and Opposite-Sex Relations in 1970 and in 1996.** Chris Magnusson

*Purpose:* To describe changes in adolescent girls' sexual attitudes and relationships with boys between 1970 and 1996, particularly girls who had early onset of sexual intercourse. *Method and Instrument:* The study includes two cohorts. The first is from the Swedish longitudinal research program, "Individual Development and Adaptation." This cohort included all eighth-grade girls (15-year-olds), 522 girls, in a mid-Swedish community in 1970. In 1996, the same instrument (Adjustment Screening Test) was administered to all eighth-grade girls (15-year-olds), 567 girls, in the same community. These girls make up the second cohort. *Results:* Girls were thinking and feeling similarly about sexual matters in 1970 and 1996. Furthermore, the same factors correlated with early sexual onset of intercourse in both cohorts, and the correlations were of about the same magnitudes. This suggests that sexuality has quite similar developmental implications in the lives at teenaged girls now as it had 25 yeas ago. There were, however, differences in the prevalence of opposite-sex relations. Compared with girls in 1970, girls in 1996 had had fewer sexual relationships and had postponed their sexual transition. *Conclusions:* This study shows that perceptual, bodily, and behavioral maturation are positively related to each other. The girls with early onset of intercourse matured early both in 1970 and in 1996. They felt sexually more experienced than their agemates, and they also aspired to be older. **J Adolesc Health** 2001;28:242–252. Reprinted by permission of Elsevier Science, copyright 2001 by The Society for Adolescent Medicine.